Variant: NM_007294.4(BRCA1):c.68_69del (p.Glu23fs)

Version: 2.0

CA003783

17662 (ClinVar)

Gene: BRCA1 (HGNC:672)
Condition: BRCA1-related cancer predisposition (MONDO:0700268)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8cc9bd83-9b2d-4a38-ba40-c2010955350d
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HGVS expressions

NM_007294.4:c.68_69del
NM_007294.4(BRCA1):c.68_69del (p.Glu23fs)
NC_000017.11:g.43124030_43124031del
CM000679.2:g.43124030_43124031del
NC_000017.10:g.41276047_41276048del
CM000679.1:g.41276047_41276048del
NC_000017.9:g.38529573_38529574del
NG_005905.2:g.93955_93956del
ENST00000354071.8:n.132_133del
ENST00000461574.2:c.68_69del
ENST00000470026.6:c.68_69del
ENST00000473961.6:c.68_69del
ENST00000476777.6:c.68_69del
ENST00000477152.6:c.68_69del
ENST00000478531.6:c.68_69del
ENST00000489037.2:c.68_69del
ENST00000493919.6:c.-20_-19del
ENST00000494123.6:c.68_69del
ENST00000497488.2:c.-219+1242_-219+1243del
ENST00000618469.2:c.68_69del
ENST00000634433.2:c.68_69del
ENST00000644379.2:c.68_69del
ENST00000644555.2:c.-219_-218del
ENST00000652672.2:c.-193_-192del
ENST00000484087.6:c.68_69del
ENST00000700182.1:c.68_69del
ENST00000700183.1:c.68_69del
ENST00000700184.1:n.311_312del
ENST00000700185.1:n.187_188del
ENST00000700186.1:n.187_188del
ENST00000357654.9:c.68_69del
ENST00000471181.7:c.68_69del
ENST00000642945.1:c.68_69del
ENST00000644555.1:c.-219_-218del
ENST00000652672.1:c.-193_-192del
ENST00000352993.7:c.68_69del
ENST00000354071.7:c.68_69del

ENST00000357654.7:c.68_69del
ENST00000461221.5:c.68_69del
ENST00000461798.5:c.68_69del
ENST00000468300.5:c.68_69del
ENST00000470026.5:c.68_69del
ENST00000471181.6:c.68_69del
ENST00000476777.5:c.68_69del
ENST00000477152.5:c.68_69del
ENST00000478531.5:c.68_69del
ENST00000489037.1:c.68_69del
ENST00000491747.6:c.68_69del
ENST00000492859.5:c.68_69del
ENST00000493795.5:c.-20_-19del
ENST00000493919.5:c.-20_-19del
ENST00000494123.5:c.68_69del
ENST00000497488.1:c.-219+1242_-219+1243del
ENST00000586385.5:c.4+1153_4+1154del
ENST00000591534.5:c.-44+1242_-44+1243del
ENST00000591849.5:c.-99+1242_-99+1243del
ENST00000618469.1:c.68_69del
ENST00000634433.1:c.68_69del
NM_007294.3:c.68_69del
NM_007297.3:c.-20_-19del
NM_007298.3:c.68_69del
NM_007299.3:c.68_69del
NM_007300.3:c.68_69del
NR_027676.1:n.229_230del
NM_007297.4:c.-20_-19del
NM_007299.4:c.68_69del
NM_007300.4:c.68_69del
NR_027676.2:n.270_271del

Pathogenic

Met criteria codes 3

PS3 **PM5_Strong** **PVS1**

Not Met criteria codes 3

BA1 **PM2** **BS1**

Evidence Links 0

Expert Panel

ENIGMA BRCA1 and BRCA2 VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen ENIGMA BRCA1 and BRCA2 Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BRCA1 Version 1.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

ENIGMA BRCA1 and BRCA2 VCEP

The c.68_69del variant in BRCA1 is a deletion of two nucleotides, predicted to encode a frameshift with consequent premature termination of the protein at codon 17 of the frameshift, or amino acid 39 (p.Glu23ValfsTer17). This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting

(PM2_Supporting, BS1, and BA1 are not met). Frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 3 leading to nonsense mediated decay (PVS1 met). The ENIGMA BRCA1/2 VCEP considered multiple lines of functional and clinical evidence to define exon-specific weights for PTC in BRCA1, and results indicate that strong evidence towards pathogenicity may be applied for a PTC variant in BRCA1 exon 3 (PM5_Strong (PTC)). Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 32546644) (PS3 met). In summary, this variant meets the criteria to be classified as a Pathogenic variant variant for BRCA1-related cancer predisposition based on the ACMG/AMP criteria applied as specified by the ENIGMA BRCA1/2 VCEP (PVS1, PM5_Strong (PTC), PS3).

Met criteria codes

PS3	ℹ	✓	Reported by one calibrated study to exhibit protein function similar to pathogenic control variants (PMID: 32546644) (PS3 met).
PM5_Strong	ℹ	✓	The ENIGMA BRCA1/2 VCEP considered multiple lines of functional and clinical evidence to define exon-specific weights for PTC in BRCA1, and results indicate that strong evidence towards pathogenicity may be applied for a PTC variant in BRCA1 exon 3 (PM5_Strong (PTC)).
PVS1	ℹ	✓	Frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 3 leading to nonsense mediated decay (PVS1 met).

Not Met criteria codes

BA1	ℹ	✗	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
PM2		✗	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).
BS1	ℹ	✗	This variant is present in gnomAD v2.1 (exomes only, non-cancer subset) or gnomAD v3.1 (non-cancer subset) but is below the ENIGMA BRCA1/2 VCEP threshold >0.00002 for BS1_Supporting (PM2_Supporting, BS1, and BA1 are not met).

Curation History

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